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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,972	01/04/2002	Jeffrey S. Bartlett	28335/36996US	9566

4743 7590 12/14/2004

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,972	BARTLETT, JEFFREY S.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,17,18,21-40 and 42-44* is/are pending in the application.

4a) Of the above claim(s) *27-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 17-18, 21-23, 25-26 and 42-44* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to an amendment filed 11/12/04. Claims 11-16, 19-20 and 41 have been cancelled. Claims 42-44 have been added. Claims 21-23 have been amended. Claims 1-10, 17-18, 21-40 and 42-44 are pending in this application. Claims 27-40 have been withdrawn. Claims 1-10, 17-18, 21-26 and 42-44 are examined herein.

Information Disclosure Statement

An IDS filed 11/12/04 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 17-18, 21-23 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an AAV2 vector with an amino acid insertion following amino acids 139, 161, 459, 584, 588 and 657, does not reasonably provide enablement for ANY AAV vector other than AAV2 with insertions at corresponding sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 12/24/03 and 8/11/04.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites an AAV vector comprising a capsid protein with an amino acid insertion in the capsid. This invention requires a complex combination of molecular cloning and viral and cell culture techniques to generate the recombinant adenovirus.

2) Scope of the invention. The invention recites very specific sites for insertion of the amino acid i.e. following the amino acid in positions 139, 161, 459, 584, 588 and 657 in SEQ ID NO:13, which is VP1 protein. These sites are based upon AAV2 as a reference sequence. The claims recite that the insertion site can be in any AAV at insertion sites that correspond to those identified in AAV2. However, the actual sites of insertion have only been identified in AAV2. Furthermore, the claims recite that "an amino acid" is inserted which covers a broad and diverse group of insertions that can be as small as a single amino acid. While, claim 10 recites that the amino acid insertion can be a targeting peptide such as CDCRGDCFC (SEQ ID NO 10), the type of amino acid that is covered by the base claim is a diverse and unrelated group of amino acids. Therefore, the recitation of "an amino acid" insertion in corresponding sequences from any AAV renders the instant invention highly unpredictable.

3) Number of working examples and guidance. The instant specification teaches means of constructing and analyzing a recombinant AAV2 vector with amino acid insertions following amino acids 139, 161, 459, 584, 588 and 657. As guidance, applicants teach that sites for insertion can be surface and secondary structural regions, which would allow targeting peptides for example to be inserted in areas that would not disrupt capsid formation. Regions to modified were identified using 1) structural information from five parvovirus 2) previous reports of immunogenic regions and random capsid mutations corresponding to AAV2 3) a model of AAV2 capsid obtained following a comparison of the primary amino acid sequence of AAV and other parvoviridae for regions of defined secondary structure (see e.g. page 11, line 6-11). In practice, scanner insertional mutagenesis of AAV2 was used to identify actual sites (see example 1, page 11-12). The types of mutations generated were classified into several groups 1) capsid mutants that did not give rise to any viral particles (Type I), 2) capsid mutants that produced non-infectious particles (Type II) and 3) capsid mutants that produced fully infectious viral particles (Type III). The Type III mutants comprised 20 of the original 38 mutations. Ultimately applicants identify six of these sites as targets for insertion, which corresponds to 6/38 or about 16%. Applicants teach that corresponding sites in other parvovirus can be extrapolated to the sites identified in AAV2 (see e.g. page 4, line 3-12).

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into specific target tissues. Manipulation of AAV for altered tropism is a new and developing art.

5) Unpredictability of the art. Chiorini et al teach the relationship of AAV4 and AAV3 to AAV2 (Journal of Virology, 1997 see Figure 3 and page 6828, column 2). The relationships

between AAV2 and the capsid proteins of AAV3 and AAV2 are 62% and 63% respectively and to Moscovy duck and goose capsid proteins the homology is 53%. The homology to other autonomous parvovirus is quite low (page 6828, column 2, paragraph 3,line 1-7).

6) Amount of Experimentation Required. The invention recites an AAV vector comprised of an amino acid insertion following amino acids 139, 161, 459, 584, 588 and 657 of AAV2. In view of the unpredictability of the art of identifying the same sites in any other AAV vector: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Response to Amendment- 112 first paragraph, lack of enablement

On pages 8-11 of the amendment filed 11/12/04 applicants traverse the Examiner's reasoning for not finding the Declaration under Rule 1.132 by Dr. Jeffrey Bartlett filed 5/27/04, which was directed against claim rejections under 35 U.S.C. 112, first paragraph persuasive. Essentially the arguments presented are the following. 1) One of skill in the art could have predicted the two-dimensional structure of AAV capsid proteins at the time of filing as the structural analysis techniques were available see page 11, line 12-22, Declaration paragraphs 3 and 5 and Figure 1 of Wu et al, Exhibit A. The two-dimensional models demonstrate that the modeled parvovirus capsid protein structure had an overall basic structure with a common area

of variation. Figure 1 of Wu et al depicts a secondary structure model of AAV2 confirms the models of the Declaration and demonstrates that the common area of variation corresponds to large surface exposed loops and is commonly located in all the parvovirus. 2) Based upon the teachings of the specification, one of skill in the art could have performed the methods of the Declaration and therefore, the Specification does support the teachings of the Declaration. Specifically, the Declaration compares primary and secondary structure of the AAV serotype based upon the knowledge of the insertion sites taught in the specification. The comparison, Figure 1 and 2 of the Declaration, substantiated location of loops exposed to the surface. 3) Kronenberg et al support the teaching in the specification by demonstrating that the insertion sites in AAV2 are predictive of insertion sites in other serotypes.

The amendment filed 11/12/04 has been fully considered but they are not persuasive. Applicants have argued that using tools available at the time of filing a person of skill in the art would be able to generate two-dimensional models of AAV capsid. This has not been in question. Rather, it is not clear from the specification and the art that these models were of probative value in actual determination of insertion sites that could be tolerated. The instant invention recites insertion sites within any AAV serotype that correspond to those specifically identified in AAV2. However, the specification is directed towards identification of insertion sites in AAV2. As the specification does not teach means of identifying "corresponding sequences" in any AAV therefore, the specification does not provide the means to identify any of the sites in other AAV vectors. Absent evidence to the contrary, there is undue experimentation to determine the relevant "corresponding sites" in any other AAV serotype. It has not been demonstrated that the models depicted in the post-filing Declaration and pre-filing Exhibit A are

adequate to be of predictive value for identifying the exact insertion sites and not just of secondary structure. Rather, to identify insertion sites applicants have actually relied on insertional mutagenesis. Wu et al performed insertional mutagenesis to generate a functional map of the AAV capsid. In so doing a functional map of the AAV2 capsid proteins was generated. While the map generated does correspond to that in the Specification, the sites that were identified as tolerant of insertional mutagenesis did not overlap with that of the instant invention. Despite comparable methods, Wu et al did not identify the same sites as the instant invention that could tolerate insertion. Given the unpredictability of the same method identifying the same sites, the lack of sequence homology between AAV serotypes in VP1, the lack of guidance in the specification, undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Finally, while the primary amino acid sequences of the three VP proteins are related, the sites that tolerate insertions are not the same in each capsid protein. Therefore, for functional purposes of tolerating insertions in the capsid protein yet forming infectious particles, the capsids are not related. Therefore, it is unpredictable that modeling of VP1 using parvovirus would generate the same kind of model system detailed for VP3. Specifically,

Claims 1-10, 17-18, 21-23, 25-26 and 42-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants claim an AAV vector with an amino acid insertion at specific amino acid sequences with a critical element that peptides or polypeptides of interest may be inserted for presentation in a desired conformation to allow for the development of AAV vectors that deliver DNA to specific target cells or display surface immunogenic peptides or polypeptides (see e.g. page 3, line 18-22). **This rejection is maintained for reasons of record in the office action mailed 12/24/03 and 8/11/04.**

Applicants claim a genus of capsid proteins with "an amino acid insertion". **This is a new rejection.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant invention, applicants recite that these sites are in positions following amino acids 139, 161, 459, 584, 588 or 657 in the VP1 capsid which sequence is presented in SEQ ID NO 13. This sequence corresponds to VP1 of AAV2. Applicants teach that surface and secondary structural regions were identified in a comparison of five parvoviruses. However, this broad and hypothetical functional characteristic was not used to identify the specific sites of AAV that could tolerate insertion mutagenesis and provide for presentation of peptides for targeting or immunogen presentation. Rather site-directed mutagenesis of AAV2 was used to identify the specific sites of insertion (see example 1, page 11-12). However, the structural

requirements of these regions to meet the functional limitations of the claimed invention are unknown. Applicants teach that these sites can be understood to be corresponding sites in other parvovirus (see e.g. page 4, line 3-12). Neither applicant nor the prior art provide a correlation between the structure of any parvovirus VP1 protein and the functional requirements for identification of sites for insertion of a peptide for representation of targeting motifs or immunogens. Chiorini et al teach the relationship of AAV4 and AAV3 to AAV2 (Journal of Virology, 1997 see Figure 3 and page 6828, column 2). The relationships between the capsid proteins are 62% and 63% and to Moscovy duck and goose 53% homology while to other autonomous parvovirus there is little homology (page 6828, column 2, paragraph 3,line 1-7). It is unclear what functional characteristics should be used to identify the sites of insertion for vectors other than AAV2. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of parvovirus capsid regions and the lack of written disclosure of the structural characteristics, and the lack of written disclosure of the functional characteristics required for the insertion sites to be identified in other parvovirus, it is concluded that applicant was not in possession of their invention.

In the instant invention, applicants claim an AAV vector comprising a capsid protein with an amino acid insertion. The specification teaches that "an insertion amino acid" can be a targeting peptide; specifically embodied insertions are amino acids of between 6 and 10 peptides (see page 12, line 4-22). Applicants state that larger peptide epitopes are thought to disrupt capsid formation (see e.g. page 22, line 15-16). However, the upper limit of amino acid sizes is never elucidated. Applicants found that linker/scaffolding sequence of two to three amino acids

at each end of the targeting peptides generate a more flexible insertion peptide, which is beneficial for capsid formation (see e.g. table 1). Applicants demonstrate that targeting peptides that are between 6 and 10 amino acids as well as a BAP insert that is 15 amino acids had varying effects dependent upon the site of insertion. However, by reciting "an amino acid" applicants recite a large and diverse group of molecules that differ in size and quality. Applicants do not provide a detailed description of the sequences such that applicants can identify the size or qualitative requirements of "an amino acid insertion". Can the insertion be a single amino acid? By reciting "an amino acid insertion", the relationship between structure and function is unclear. As there is no correlation between the structure of the recited sequences and their ability to insert into the capsid such that the capsid can form and the vector can form an infectious particle. Given the diversity and large size of amino acid insertions, and the inability to determine which will function as designated, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Amendment- 112 first paragraph, lack of written description

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 11 to 12 of the amendment filed 11/12/04. Applicants argue essentially the following. 1) The working examples of the specification teach insertion of peptides into the AAV2 capsid. Due to the similarity of the secondary structure of the capsid protein of the genus AAV, one of skill would understand that applicants were in possession of the ability to make the AAV genus of

insertions. 2) The specification identifies regions of insertion and specific sites within AAV2 that are amenable to insertions and the Declaration provides evidence that corresponding insertion sites in any AAV can be identified. 3) The specification teaches 20 insertion sites which are a representative number of species of the claimed genus. The claims are directed toward corresponding insertion sites in other serotypes. Given that the amino acids of the AAV serotypes are known, the corresponding amino acids insertion sites can be identified.

Applicants' arguments filed 11/12/04 have been fully considered but they are not persuasive. While applicants have disclosed the genus of AAV2 insertion sites, the genus of AAV vectors with corresponding insertion sites has not been disclosed and a person of skill in the art would not have been able to envision the claimed genus given the state of the art at the time of filing. Specifically, the specification has provided no direction for the construction of insertions into any AAV serotype except AAV2. Furthermore, there is no indication that despite the fact that the amino acids of many AAV serotypes are known, the corresponding amino acids insertion sites have been identified or could be identified to date. Applicants recite a broad and loosely related genus of AAV vectors. The relationships between AAV2 and the capsid proteins of AAV3 and AAV2 are 62% and 63% respectively and to Moscovy duck and goose capsid proteins the homology is 53%. The homology to other autonomous parvovirus is quite low (page 6828, column 2, paragraph 3, line 1-7). By disclosing the sites of AAV2 capsid proteins that tolerate insertions and yet form infectious particles, applicants have not demonstrated that they were in possession of the larger genus of AAV vectors with insertions. Applicants' have argued that they were in possession of the ability **to make** AAV vector with insertions into the AAV capsid protein. The rejection of the claims under 35 USC 112, first for lack of written

description is not based upon whether the insertions can be made rather whether the applicants were in possession of the recited genus. In the instant case, the disclosure of AAV2 insertion sites does not constitute written description for insertion sites in any AAV serotype. The skilled artisan cannot envision the detailed structure of the broad class of AAV serotype insertion sites regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it.

Conclusion

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-10, 17-18, 21-23, 25-26 and 42-44 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

November 23, 2004

GERRY LEFFERS
PRIMARY EXAMINER